Subklinik Hipotiroidili Hastalarda Tedavi Öncesi ve Tedavi Sonrası Oreksin A Düzeylerinin Karşılaştırılması

Comparison of Pre and Post-Treatment Orexin A Levels in Patients with Subclinical Hypothyroidism

Subklinik Hipotiroidili Hastalarda Oreksin A Düzeyi / Orexin A Levels in Patients with Subclinical Hypothyroidism

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Özet

Amaç

Subklinik hipotiroidi, görülme sıklığı yaşla birlikte artan ve kadınlarda daha fazla görülen klinik bir durumdur. Subklinik hipotiroidide uyku, iştah problemleri ve değişik yakınmalar görülebilmektedir. Oreksinler kardiyovasküler işlevlerin düzenlenmesi, uyku-uyanıklık döngüsünün ayarlanması gibi birçok fizyolojik düzenlemede rol alır. Oreksinlerin fizyolojik düzenleme alanlarının hipotiroidizmin klinik bulguları ile benzerlik göstermesi bu araştırmanın planlanmasında etkili oldu. Bunun yanında kardiyovasküler sistem üzerine etkili ve oreksinler gibi yemek yeme ile plazma seviyesi değişen homosisteine de bakıldı. Ayrıca hastaların lipid profillerindeki değişiklik de gözlendi.

Gereç ve Yöntemler

Subklinik hipotiroidisi olan menopoz öncesi dönemde ki 19 bayan hasta (ortalama yaş=39.58±12.58, ortalama BMI= 26.7±4.9) çalışmaya dahil edildi. 12 saatlik açlıktan sonra hastaların kanları alındı. Çalışmaya katılan tüm hastalara başlangıçta 50µg/day L-T4 verildi ve daha sonra 4-6 haftalık takiplerle gerekli doz ayarlamaları yapılarak ötiroid hale gelmeleri sağlandı. 4 ay sonra ötiroid hale geldiklerinden emin olunduktan sonra tekrar kanları alındı ve değerlendirildi.

Bulgular

19 premenopozal subklinik hipotiroidili hastanın tedavi öncesi oreksin seviyeleri, l-tiroksin ile 4 aylık tedaviden sonra istatistiksel olarak anlamlı oranda yükseldi (te-

Summary

Aim

Subclinical hypothyroidism is a clinical condition mostly observed in women, the prevalence of which increases by age. Sleepiness and appetite problems are observed in subclinical hypothyroidism. Orexins play a role in the physiological regulations like the stabilization of cardiovascular functions and the sleep-alert cycle. Similarities in the physiological regulation areas of orexins and the clinical findings of hypothyroidism were influential in the planning of this research. Additionally, homosisteine, which is influential on the cardiovascular system and the plasma level of which changes by eating (as is the case with orexins), was also analyzed. Besides, the change in the lipid profiles of the patients was also observed.

Material and Methods

Nineteen pre-menopausal female patients (mean age=39.58±12.58, mean BMI= 26.7±4.9) included in this study. Following 12 hours fasting blood samples were taken from brachial vein. All patients were given 50µg/day L-T4 TSH levels were examined in every 4-6 weeks to adjust the L-T4 doses. When euthyroidism was ensured, a re-evaluation was made 4 months later.

Results

Pre-treatment plasma orexin A levels of 19 patients with pre-menopausal subclinical hypothyroidism increased significantly following a treatment of l-tiroxin for 4 months (pre-treatment orexin level median=1.20

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davi öncesi oreksin seviyesi median=1.20 mg/dl (ortalama 1.33±0.28) tedavi sonrası median=1.82 mg/dl (ortalama 1.70±0.42) p=0.007). Plazma total homosistein seviyesinde ve lipid profilinde anlamlı bir değişiklik saptanmadı.

Sonuç

Oreksin seviyelerinin subklinik hipotiroidi vakalarındaki fizyolojik etkileri ve tedavide olası yararları konusunda ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler

Oreksin A, Subklinik Hipotiroidi, TSH, Homosistein.

mg/dl (mean: 1.33±0.28) post-treatment median=1.82 mg/dl (mean: 1.70±0.42) p=0.007). A significant change in the level of plasma total homosisteine and lipid profile was not detected.

Conclusion

Advanced studies are needed to study the physiological effects of orexin levels in cases with subclinical hypothyroidism and the possible benefits in treatment.

Keywords

Orexin A, Subclinical Hypothyroidism, TSH, Homocysteine.

Introduction

Subclinical hypothyroidism (SH) is a condition the diagnosis of which is made when the serum thyroid stimulating hormone (TSH) level is above the reference value (0.45-4.5 mIU/L) and the free thyroid hormones are in normal levels [1-3]. It is generally encountered in adults, especially in women of 60 years or above [4]. While the prevalence of subclinical hypothyroidism is about 4-8.5%, this rate goes beyond 20 % for the women above 60 years of age [3]. Although the mostly blamed factor in the etiology is chronic autoimmune thyroid diseases; partial thyroidectomy, application of radiotherapy to head and neck, and the use of amiodarone, lithium and fenotiasine group medicines play a role as well [5].

A consensus is ensured regarding the diagnosis of subclinical hypothyroidism; but discussions about its treatment still continue [3,6]. Studies reporting that somatic and neuropsychiatric symptoms are relieved by treatment and that lipid profile turns back to normal, recommend that it should be treated [7,8]. However, the studies, which point that complications arising out of TSH suppression (atrial fibrillation and osteoporosis etc.) are more dangerous, are against the treatment [9,10]. General tendency is to treat the subclinical hypothyroidism with tiroxin if serum TSH level is higher than 10 mIU/L. When the TSH level is between 5-10 mIU/L, the treatment should be arranged according to the individual characteristics considering the existence of antithyroid antibodies and the clinical factors [2,3].

Orexins (orexin A, orexin B) are also known as hypocretines. Orexins of peptide structure that are identified in the rat hypothalamus are formed as a result of proteolysis of the precursor prepro-orexin containing 130 amino acids [11]. They are named as orexin, which means appetite as they stimulate feeding when they are applied ICV (intracerebrovascular) [12].

Dr. Glenda Harris et al. searched the functions of orexin secreted from the brain cells in hypothalamus under the aegis of Pennsylvania University. This part of the brain plays role in many vital functions like eating, body temperature, fat metabolism. Orexin neurons in the lateral hypothalamus are tightly related to eating and drinking actions. However, the orexin neurons in perifornical and dorsomedial hypothalamus play role in the regulation of the response to stress [13].

Following these researches, it is seen that orexins take part in many physiological functions like the regulation of the cardiovascular functions, the sleepiness-wakefulness cycle, getting thirsty and nociception [11].

Homosisteine is an essential amino acid that is formed during methionine metabolism, not involved in the structure of proteins and synthesized out of methionine in the body. It is mainly metabolized via two ways, which are remetilation and trans-sulphuration [14]. Diekman et al. stated that concentration of plasma total homocysteine increases in hypothyroidia [15]. The same study expresses that fT4 is an independent determinant factor in the plasma for total homocysteine.

The correlation between orexin and TSH is put forth by few researches in the literature [16]. Additionally, orexin and thyroid hormones having a common area of influence like the regulation of appetite and sleep is the starting point of the research on the orexin levels in the patients with subclinical hypothyroidism.

We aimed at researching whether there is a correlation among TSH, orexin and homocysteine that have many common physiological areas of influence and secreted from close locations via controlled clinical experiment method in this study. We also planned to observe the changes in the lipid profile.

Material and Methods

Nineteen pre-menopausal female patients (mean age=39.58±12.58, mean BMI= 26.7±4.9) included in this study were examined and followed by the Department of Endocrinology and Metabolism, Gülhane Military Medical Academy. The patients were restricted from eating for one night and then a complete medical evaluation besides laboratory tests were made to exclude non-thyroidal diseases. Criteria for exclusion from the study were: coronary arterial disease, pituitary/hypotalamic diseases and other non-thyroidal diseases. None of the patients took vitamins, lipid lowering medications or etc. going into interaction with homocysteine metabolism, lipid profile and thyroidic function. Written consent was taken from all patients.

Patients with normal tiroxin levels at the end of two measurements and TSH concentrations above 5 mIU/L, were identified as SH [21]. The underlying diseases were detected to be autoimmune thyroiditis as a result of the investigations that were carried out besides the observation of the patients.

Following 12 hours fasting (between 20:00-09:00) blood samples were taken from brachial vein. All patients were given 50µg/day L-T4 (Levotroksin®, Abdi İbrahim, Türkiye). TSH levels were examined in every 4-6 weeks to adjust the L-T4 doses. The necessary average level of L-T4 was 85±30 µg/day to ensure euthyroidism. When euthyroidism was ensured, a re-evaluation was made 4 months later.

Venous blood samples were stored at -70ºC until the date of the research. Levels of Serum TSH, free-T4, free Triiodothyronine (f-T3) (Immulite 2000 autoanalyzer by BIO-DPC, CA, USA) and total cholesterol, trigliserid and high-density lipoprotein (HDL) cholesterol levels (Olympus AU 2700 auto analyzer, Germany) were studies via commercially accessible methods. LDL (low-density lipoprotein) cholesterol was calculated by the Friedewald formula. Homocysteine (t-Hyc) levels were detected by high pressure liquid cromotography (normal range: 5-12 mmol/L; intra-measure coefficient variety: %0.4-5).

Interviews were held with patients in periods of four to six weeks and sleep, appetite condition, changes in weight, intestinal problems and general complaints of the patients were evaluated in these interviews besides the changes needed in l-tiroxin doses.

19 patients participated in the whole process of this research. None of them abandoned the research for any reason.

The data that were analyzed with the help of SPSS 11.0 program with the Wilcoxon signed ranks test because the data was not fitting to normal distribution. Values were given as medians.

Results

Means and average values of the data are given in Table 1. Orexin A level became meaningfully higher following the treatment with L-tiroxin than the pre-treatment level (p=0.007). Pre-treatment values of orexin were minimum=1.00, maximum=1.93 median=1.20 (average=1.33±0.28). Post-treatment values became minimum=1.02, maximum=2.72, median=1.82 (average=1.70±0.42).

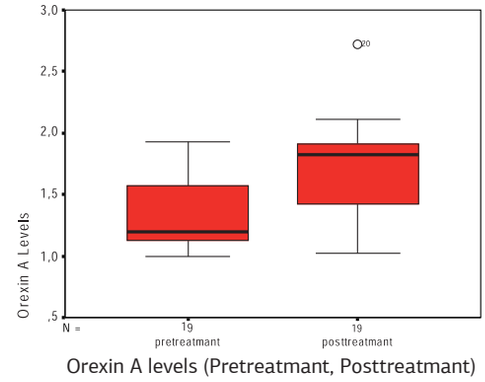
Post-treatment TSH levels got meaningfully lower than the pre-treatment levels as expected (p<0.001). While the pre-treatment median for TSH was 8.20 mIU/L, its post-treatment level became 1.20 mIU/L. Free T4 level had a significant increase (p<0.001). While the pre-treatment median was 0.90 pg/ml, its post-treatment level became 1.30 pg/ml.

Besides this, no statistically significant change was observed in the levels of total cholesterol, ldl cholesterol, hdl cholesterol, trigliceride and fT3, for which different conclusions were driven in different studies. Plasma homocysteine levels of our patients with subclinical hypothyroidism were in normal levels. Similarly, no statistically significant change was detected for homocysteine levels (Table 1).

Table 1. Clinical Characteristics of Patients

Variable	Pretreatment (n:19) (Mean±SD**)	Posttreatmant (n:19) (Mean±SD)	*P* ***
BMI (kg/m^2)*	26.7±4.9	26.3±4.7	*P* >0.05
f-T4 (pg/ml)	0.88±0.16	1.38±0.26	*P* <0,001
f-T3 (ng/dl)	2.84±0.37	3.12±0.7	*P* >0.05
TSH (mIU/L)	10.10±5.28	1.57±1.28	*P*< 0,001
Total Cholesterol (mg/dl)	199.1±39.1	201.6±40.9	*P* >0.05
Triglycerides (mg/dl)	149.5±97.2	124.0±57.2	*P* >0.05
LDL Cholesterol (mg/dl)	123.2±31.9	134.8±38.3	*P* >0.05
HDL Cholesterol (mg/dl)	49.7±14.8	48.9±13.7	*P* >0.05
Orexin (ng/ml)	1.33±0.28	1.70±0.42	*P* =0.007
Homocysteine (mmol/L)	10.2±3.3	9.5±2.8	*P* >0.05

*BMI: Body Mass Index, **Standard Deviation, *** Wilcoxon Sign Ranks Test.



Orexin A levels (Pretreatmant, Posttreatmant)

Discussion

Orexin A, which is a strong agonist of Orexin1 (OXR1) and orexin2 (OX2) receptors, is a recently-discovered neuropeptide. Orexin A and receptors are found in great numbers in the central nervous system and peripheral organs. Orexin A plays a variety of roles in ingestion and energy metabolism. Besides, it plays a great role in the regulation of hypotalamo-pituitary axis. The role of orexin A in the regulation of hypotalamo-pituitary-adrenal, -thyroid, -somatotropic and –gonadal axis could not have been adequately researched [17].

There are few studies regarding the correlation between orexin and thyroid hormone. Orexin A is seen to inhibit the release of TRH in hypothalamus in a study carried out on rats. Plasma TSH levels had a significant decrease in comparison

with the dose after 15 minutes following the intravenous injection of orexin A. No change was observed in the levels of plasma thyroid hormone [16].

The expression of the thyroid hormone and prepro-OX secreted by rat hypotalamus besides the orexin receptor (OXRs) secreted by hypotalamus and adrenal gland was researched in 2001 and no significant difference could be found [18].

However, we found significantly high levels of post-treatment orexin compared to the pre-treatment levels in our research. This made us to consider that TSH levels decreasing by L-tiroxin treatment or increasing thyroid hormone levels might trigger the release of orexin. Additionally, even the question whether the thyroid hormones exert some of their effects via orexin is considered.

It is known that the orexin 1 receptor resembles the TRH receptor in structural terms by 25% and that orexin A is an agonist of high affinity for OXR1 [19]. Could this affinity have a role in the increase of the plasma orexin A level with L-tiroxin treatment in subclinical hypothyroidism? More detailed researches carried out on a greater number of cases are needed in order that this question and the like can be answered.

Orexin has a major role in sustaining the state of wakefulness in mammals. Permanent damage in orexinergic function; in humans, rodents and dogs is the pathophysiological sign of narcolepsia [20].

It should not be disregarded that the orexin levels may have a role in sleepiness and decrease in appetite for the patients with subclinical hypothyroidism. It is indicated in many researches that the increase in orexin has an appetizing and sleep regulating effect [11,12,20]. It is seen in this research that an improvement is observed in appetite and sleeping conditions for the patients following the treatment of subclinical hypothyroidism in the interviews carried out during the examinations and follow-ups of these patients.

There are studies pointing that subclinical hypothyroidism has a negative effect on the lipid profile [7,8]. According to some authors, this negative change on the lipid profile should be taken into consideration while planning a treatment for subclinical hypothyroidism. However, there are also publications reporting that the treatment of subclinical hypothyroidism with L-tiroxin does not bring about any change in the lipid profile [21]. Neither did we observe any statistically significant changes regarding the lipid profile following the treatment of subclinical hypothyroidism with L-tiroxin in our study. We are of the opinion that the dislipidemia that can be seen in subclinical hypothyroidism cannot be healed only by L-tiroxin treatment. Lipid lowering medications may be useful.

Plasma total homocysteine level did not point to a statistically significant change by the transformation of subclinical hypothyroidism into euthyroid in our study in accordance with the literature [21-23]. It is also reported that the homocysteine level which is an important and independent risk factor for cardiovascular diseases is high in hypothyroidics and that it paves the way for cardiovascular-based death cases for these patients [24]. However, homocysteine levels of the patients with subclinical hypothyroidism were in normal range in our research. According to the conclusions of this study, the role of the concentration of plasma total homocysteine in the cardiovascular cases in which subclinical hypothyroidism paves the way for, is considered to be not important.

Does the alleviation of symptoms in subclinical hypothyroidism cases with tiroxin replacement treatment depend on the increase of orexin A levels more than metabolic changes? This speculation is thought to be worth searching.

Treatment of subclinical hypothyroidism leads to a meaningful increase in the level of plasma orexin A.

Low levels of orexin A may have a role in sleeping irregularities and appetite problems accompanying the insufficiency of thyroid hormone.

The role of homosisteine needs advanced researches on the cardiovascular cases in subclinical hypothyroidism patients.

The role of the correlation between the plasma orexin levels and clinical findings needs advanced researches on the treatment and follow up of subclinical hypothyroidism orexin A.

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